The Microbe Blotter: **Multiple Arrests Made**

A Patient with Fever after Chemotherapy

(PART 2)

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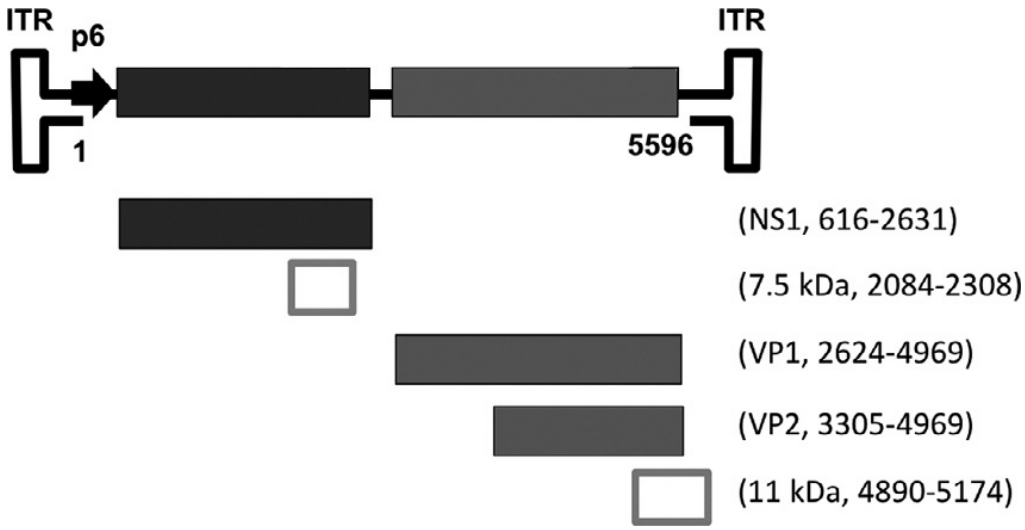
Special ID Grand Rounds

May 4, 2017

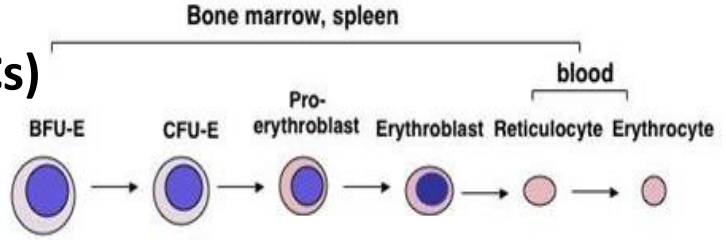
Human parvovirus B19

- Small, non-envelope, single stranded DNA virus (*Parvoviridae*)
- Extremely resistant to physical inactivation
- Important viral proteins - structural proteins VP1, VP2,

  - nonstructural proteins NS1, 11kDa, 7.5kDa



- Strong tropism to **erythroid progenitor cells (EPCs)**

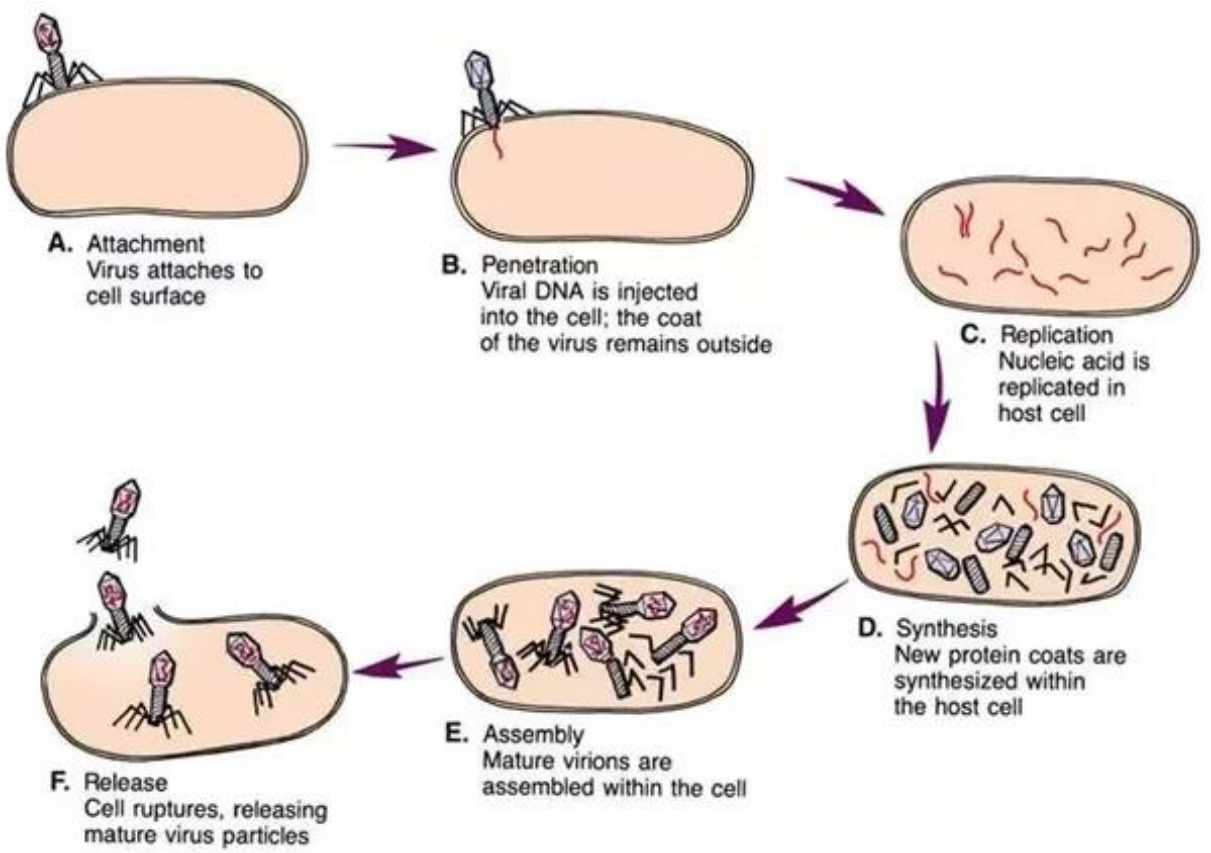


Adamson-Small L.A. et al., Virus Res. 2014; 190:8-16

Questions:

- 1. Why is Parvovirus B19 tropic for certain cell types?
- 2. What are the effects of B19 on erythroid precursors (or other cells impacted by infection), and what is their pathogenesis?
- 3. What clinical significance, if any, is proposed as the result of long-lasting B19 infection?

Virus entrance into a host cell



1. Attachment
2. Penetration
3. DNA replication
4. Protein translation
5. Assembly of virions
6. Cell lysis

Factors responsible for tropism of B19 infection

- Receptor **P antigen** (globoside, Gb4): binding

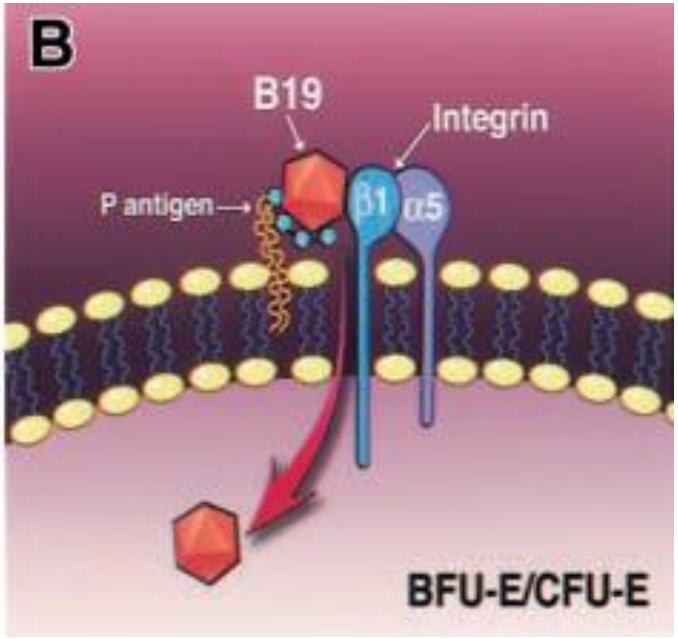
  {Brown KE, Anderson SM, Young NS; 1993}

- Co-receptors: binding and entry

  α5/ß1-integrin {Kirsten A et al; 2003}

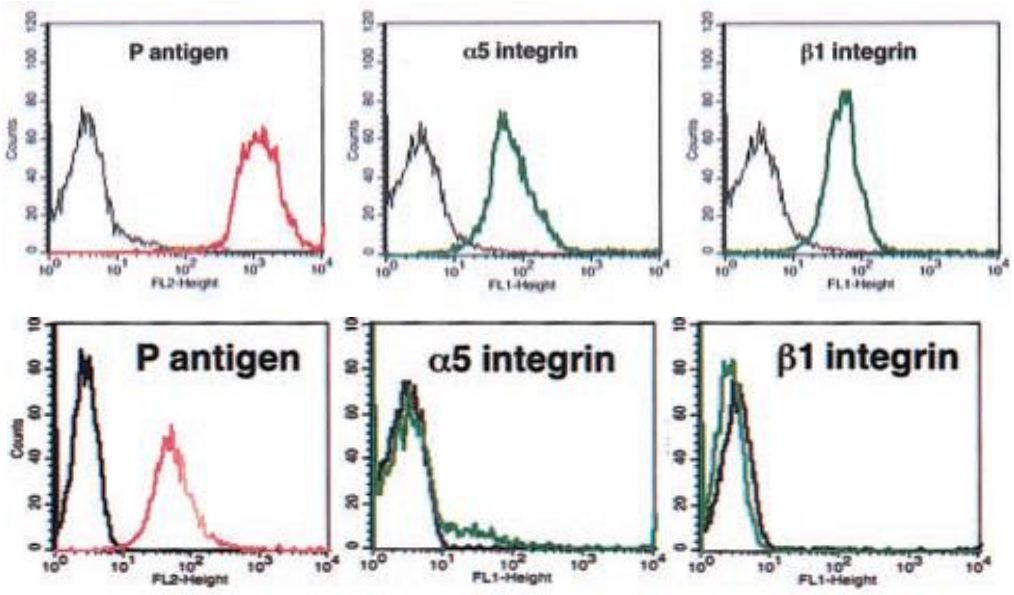
  Ku80 {Munakata Y et al; 2005}

- **Erythroid progenitor cells (EPCs)**



Weigel-Kelly K.A. et al., Blood. 2003; 102(12):3927-33

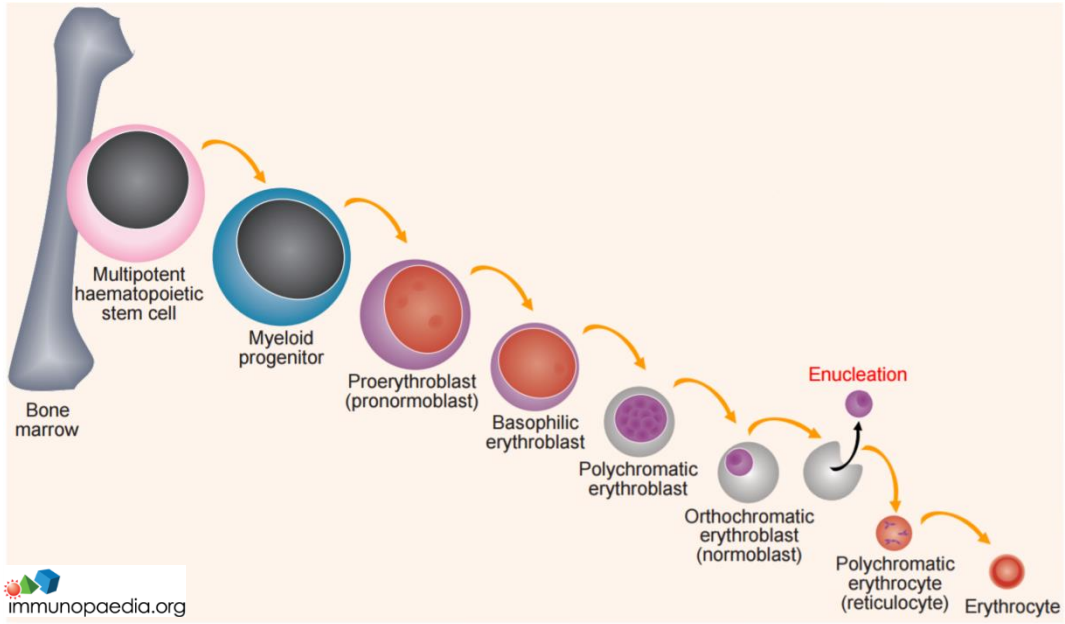
B19 replication is occurs in the cell nucleus



Primary human erythroid cells

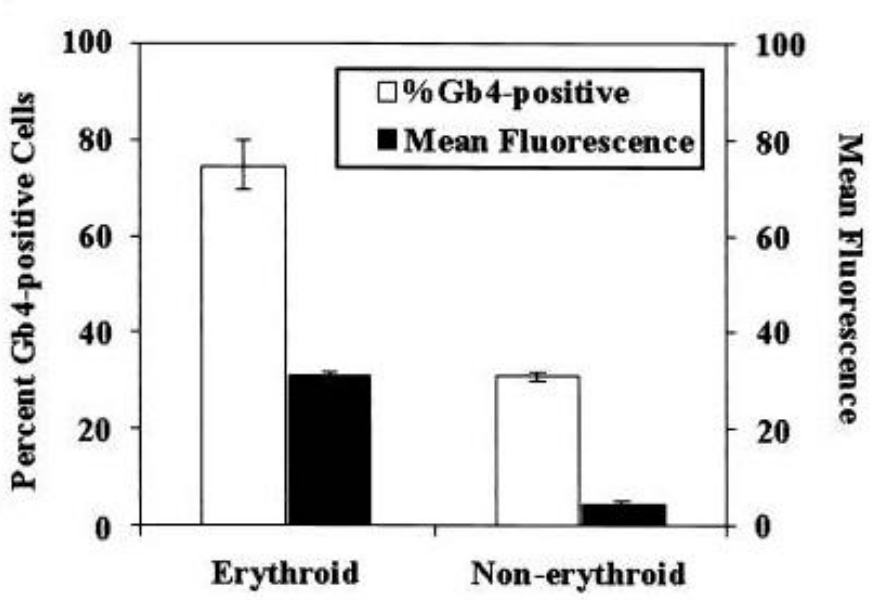
Mature human RBCs

Weigel-Kelly K.A. et al., Blood 2003; 102(12):3927-33



P antigen is present also on non-erythroid cells

P antigen (Gb4) expression



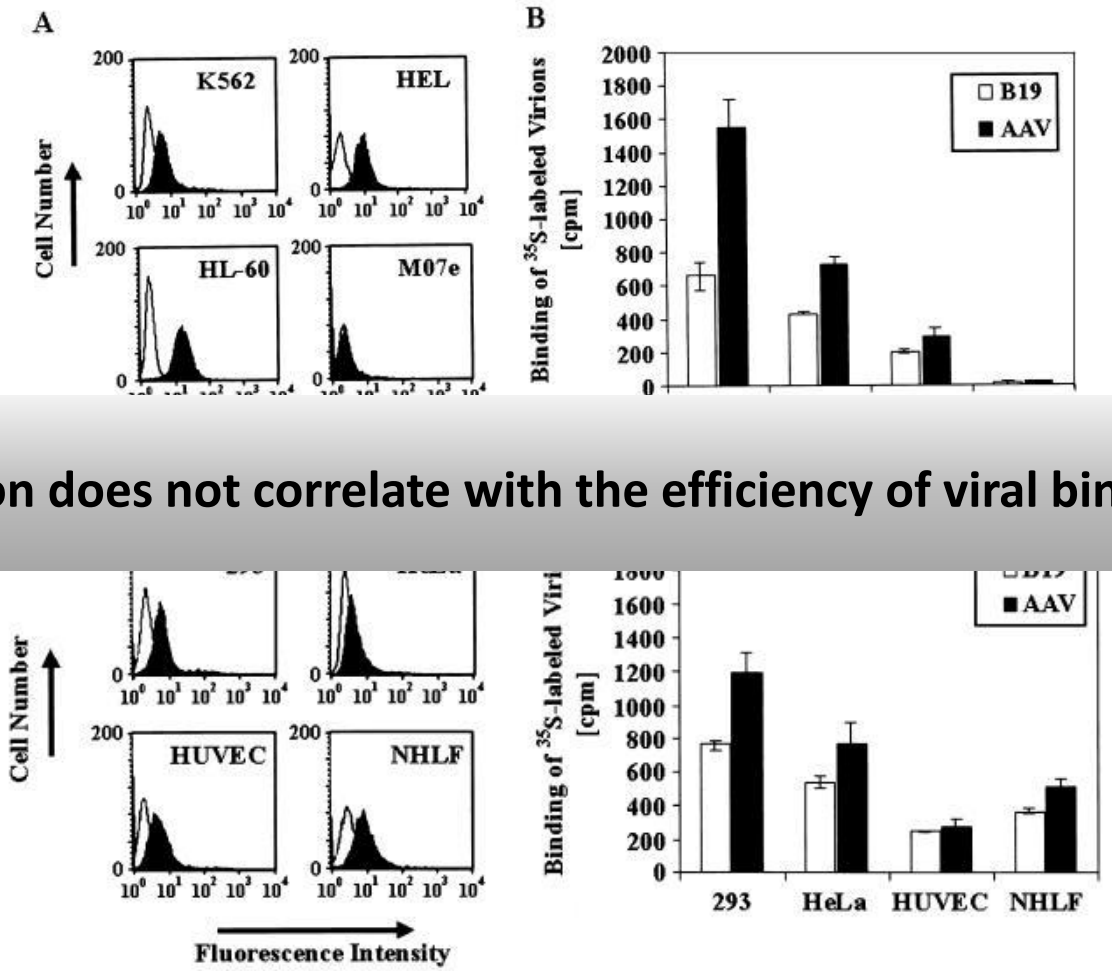
- megakaryocytes
- endothelial cells
- placenta
- fetal liver
- heart cells

Not all P antigen-expressing cells are permissive to infection by B19

Kirsten A. Weigel-Kelly et al., J Virol. 2001; 75(9): 4110–4116

Human hematopoietic cell lines

P antigen expression **Viral binding**



Level of P antigen expression does not correlate with the efficiency of viral binding

Kirsten A. Weigel-Kelly et al., J Virol. 2001; 75(9): 4110–4116

Factors responsible for tropism of B19 infection

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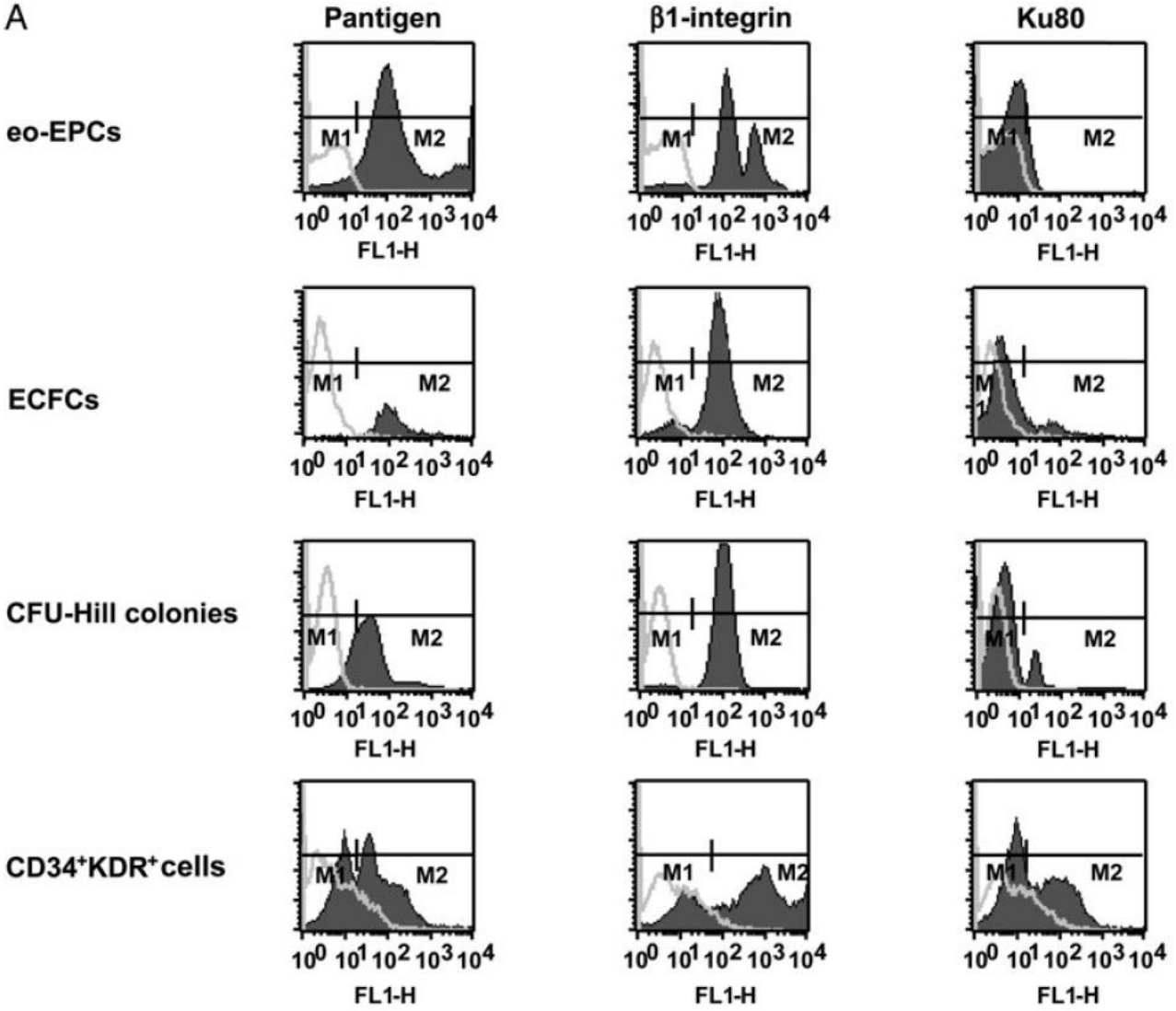
- **Erythroid progenitor cells (EPCs)**
- **Circulating angiogenic cells (CACs)**

CACs – receptor & co-receptors



eo-EPCs = early outgrowth epithelial progenitor cells
ECFCs = endothelial colony-forming cells
CFU Hill = colony-forming unit Hill
KDR = kinase insert domain receptor

Schmidt-Lucke C. at al., J Infect Dis. 2015; 212(7): 1070-81

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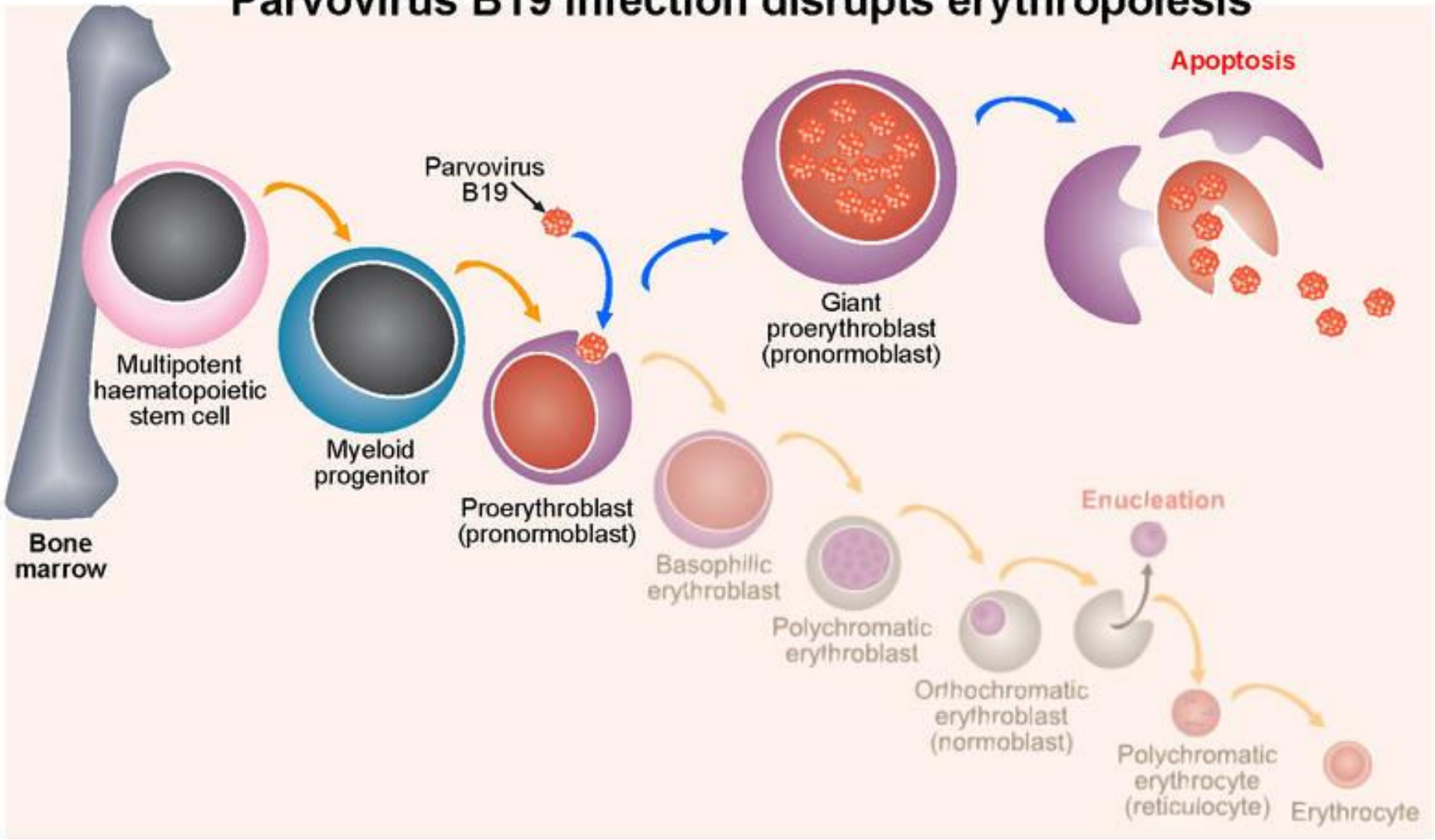
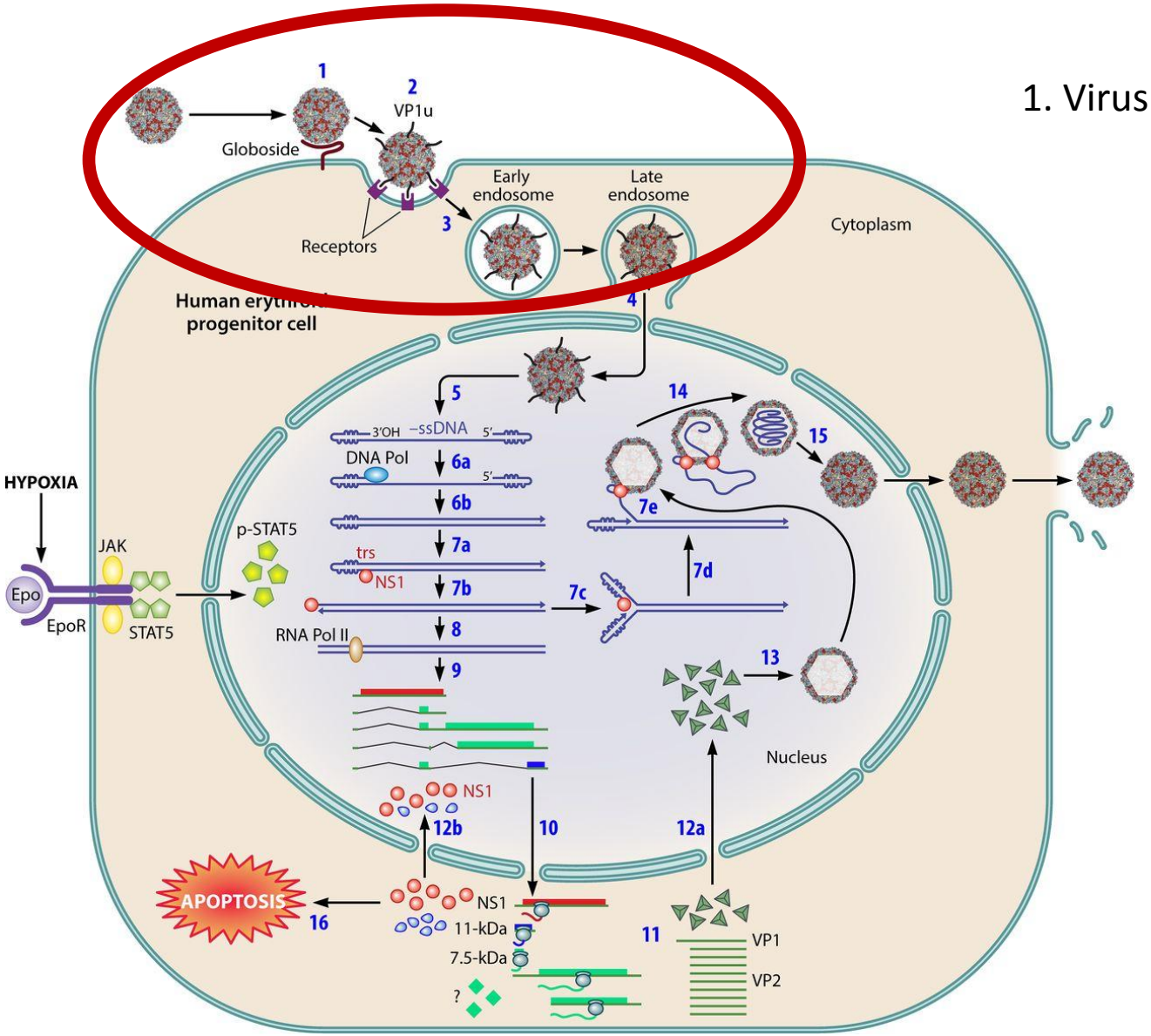
Parvovirus B19 infection disrupts erythropoiesis



How…?



1. Virus internalization into the cell

Jianming Qiu et al., Clin. Microbiol. Rev. 2017;30:43-113

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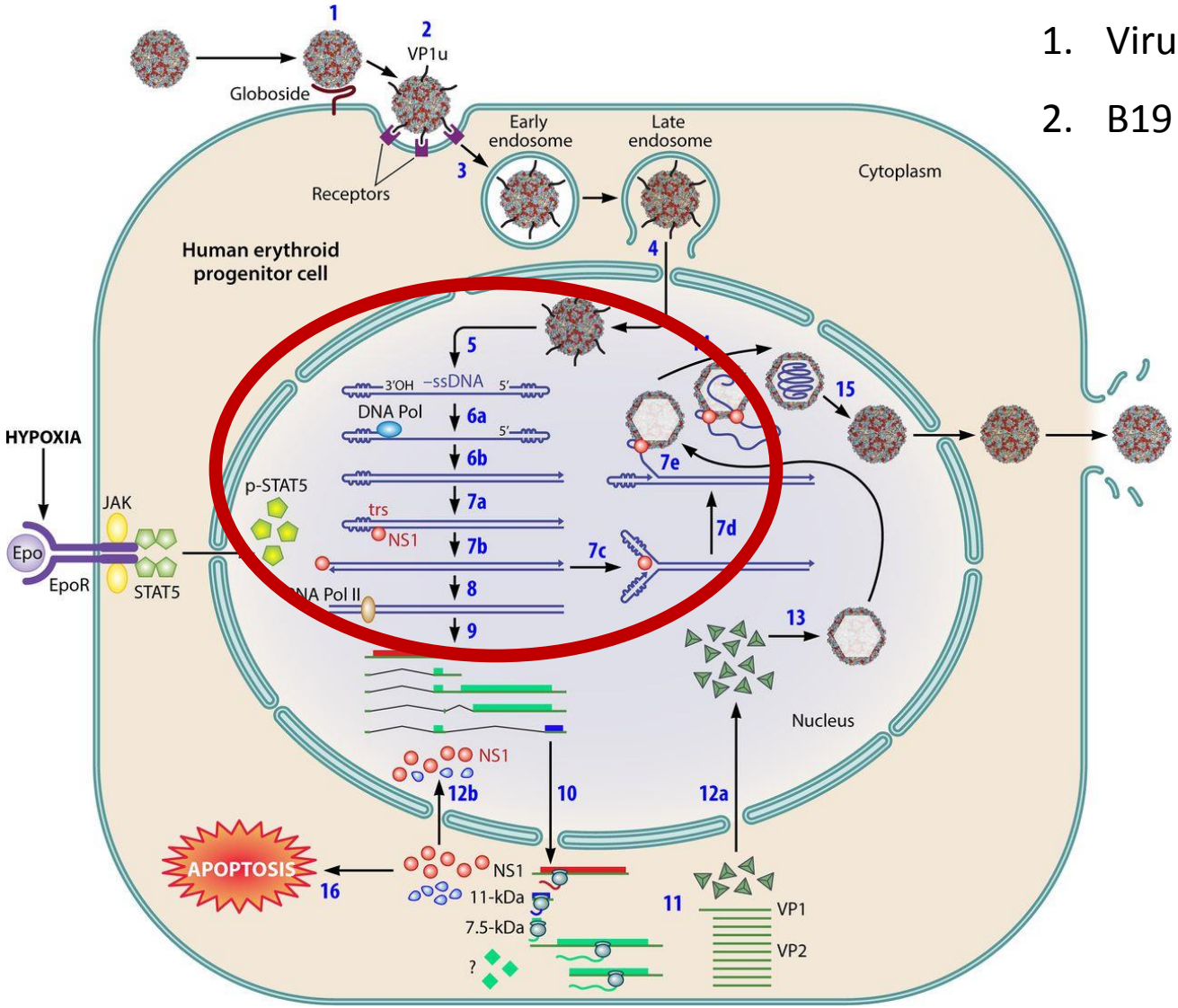

1. Virus internalization into the cell
2. B19 DNA replication

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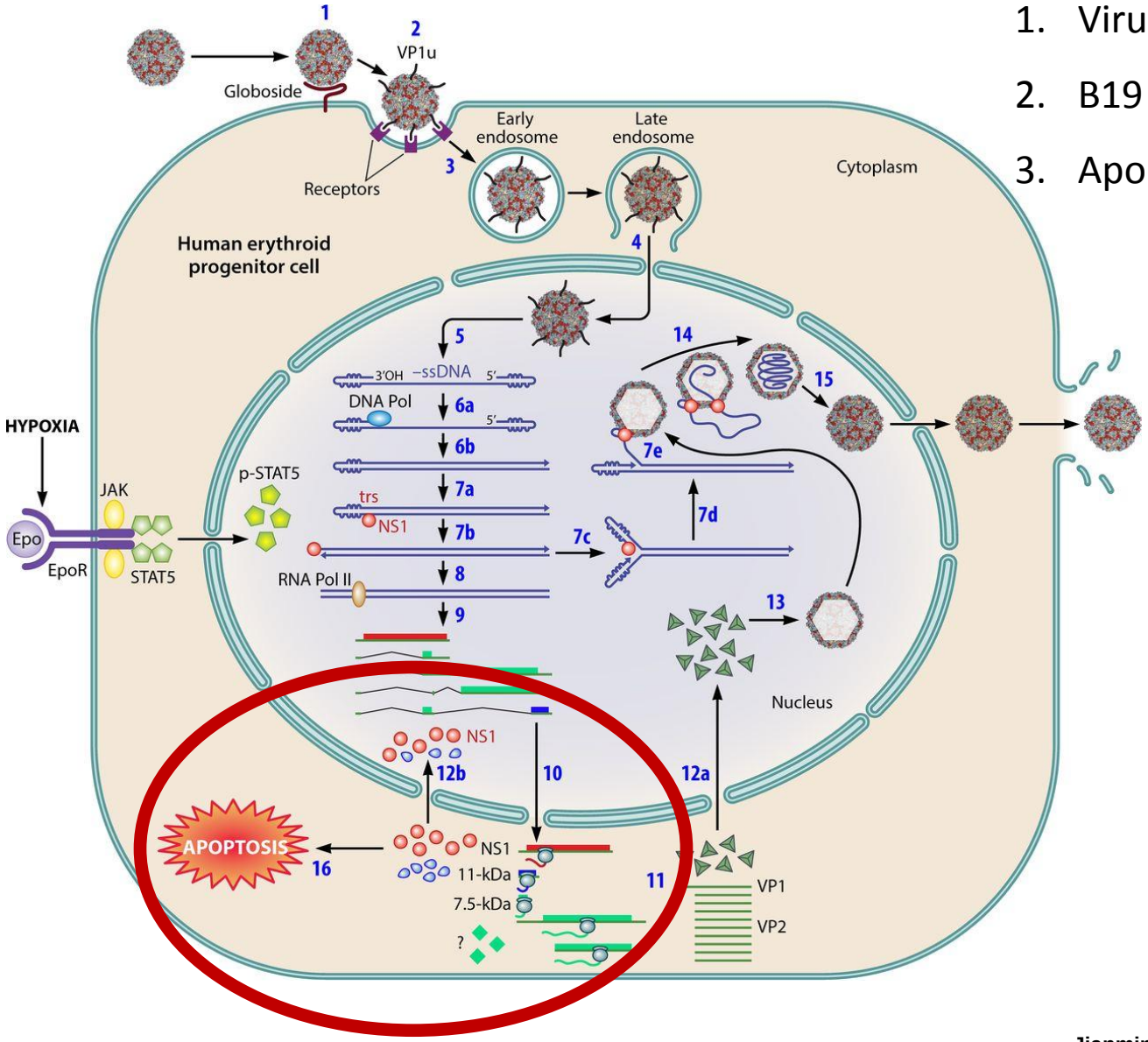


1. Virus internalization into the cell
2. B19 DNA replication
3. Apoptosis induction

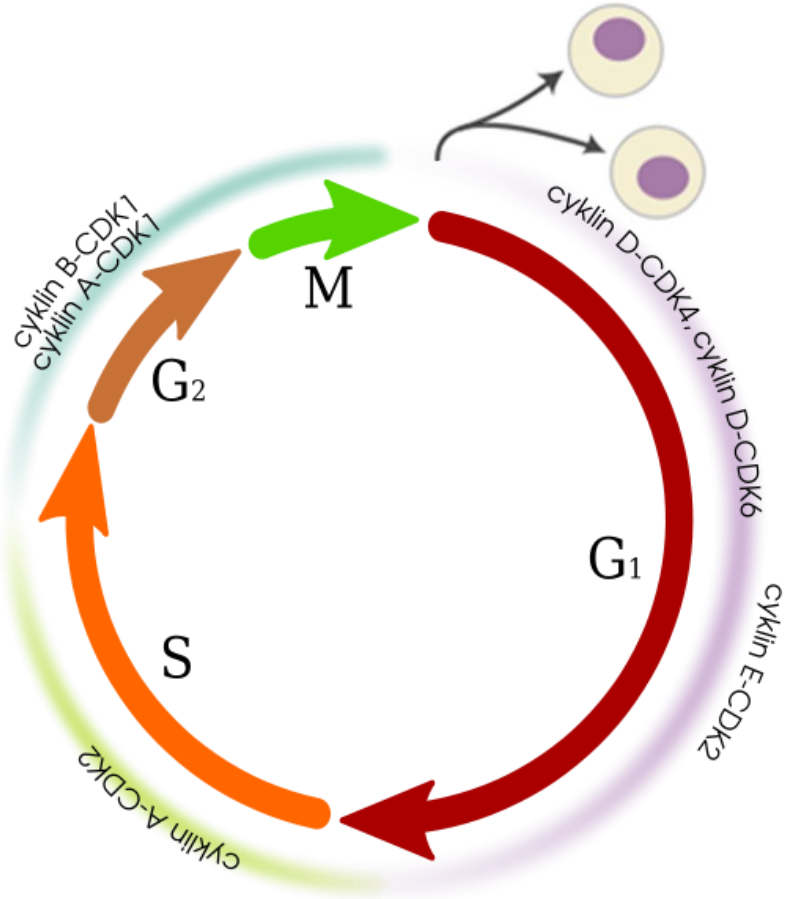
Jianming Qiu et al., Clin. Microbiol. Rev. 2017;30:43-113

THE MICROBE BLOTTER

Multiple Arrests Made

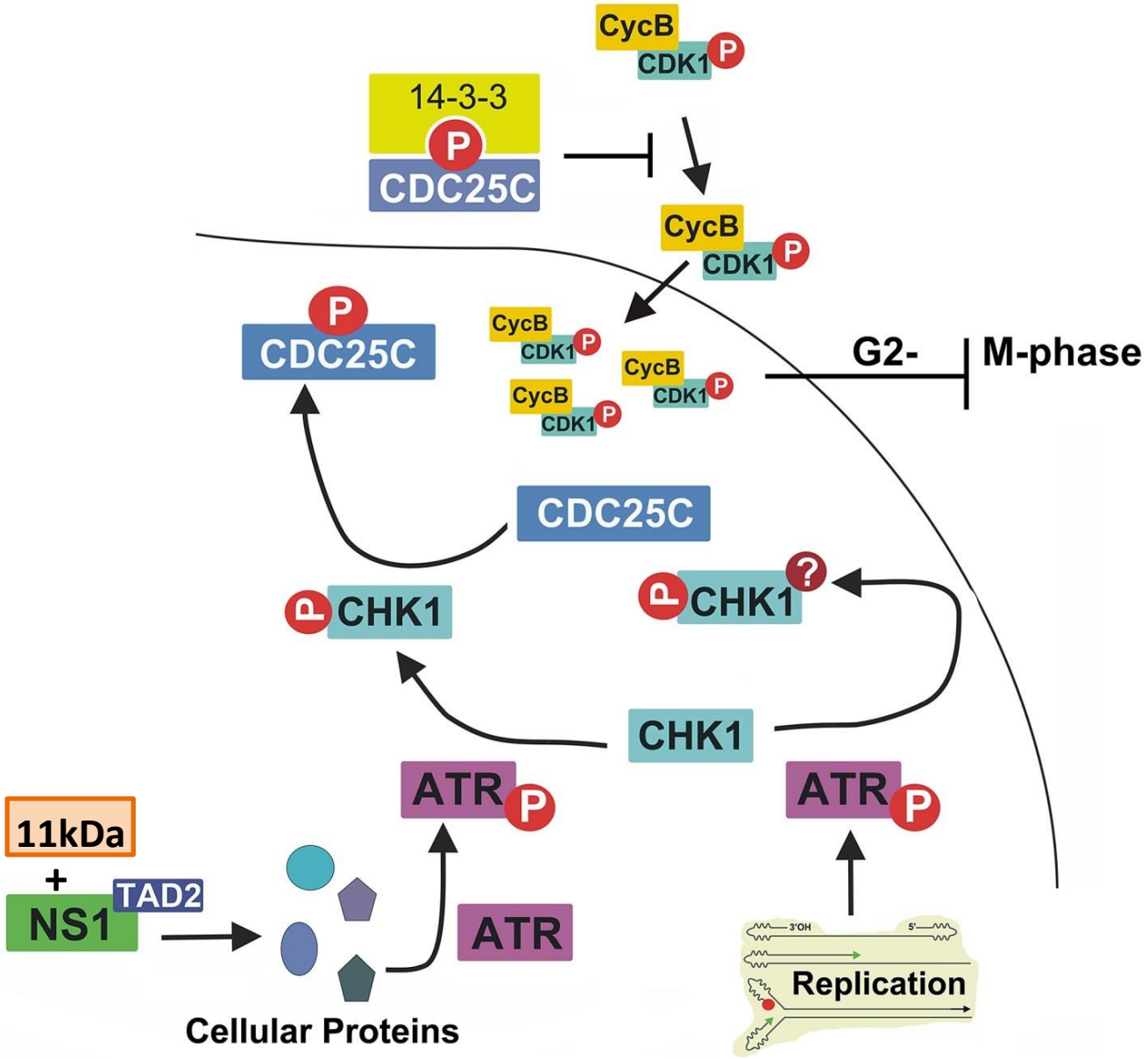
S phase
- DNA is replicated

G_2 phase
- Preparation for mitosis
- Rapid cell growth and protein synthesis
- the end of G_2 phase and mitotic entry is determined by a threshold level of active cyclin B1/CDK1 complex



NS1 and 11kDa protein induce cell cycle arrest

NS1-induced G_2 phase arrest & ATR-CDK1 pathway



Peng Xu et al., PLOS Pathog. 2017:13(3):e1006266

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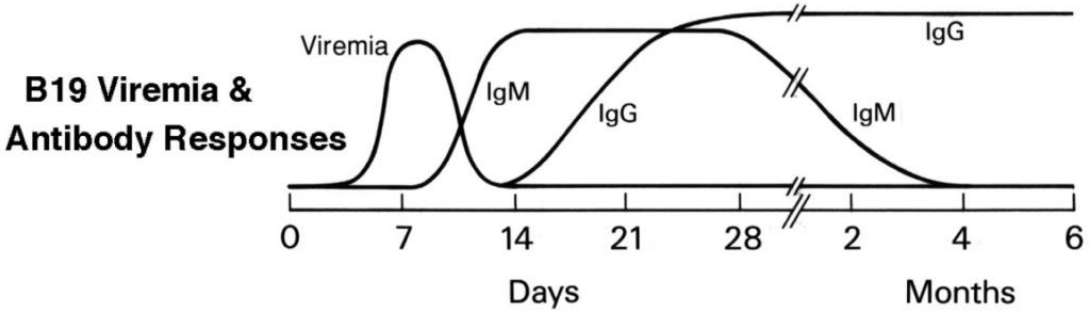
Persistent B19 infection

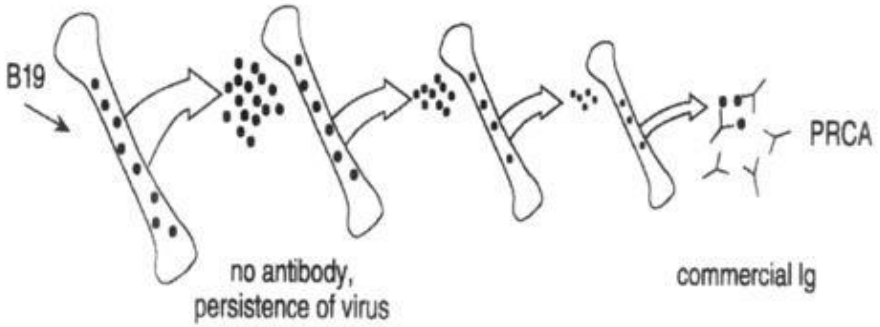
= viral DNA is present more than 6 months after onset of symptoms

Acute >10^{12} IU/mL
Persistent < 10^{4} IU/mL

Immunocompromised individuals

No neutralizing antibody
Chronic red cell aplasia





Young NS and Brown KE, N Engl J Med. 2004; 350:586-597

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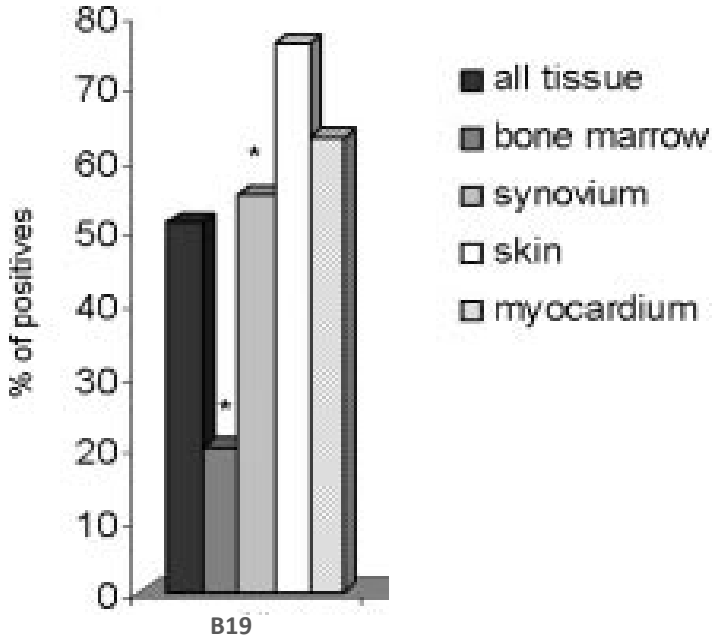


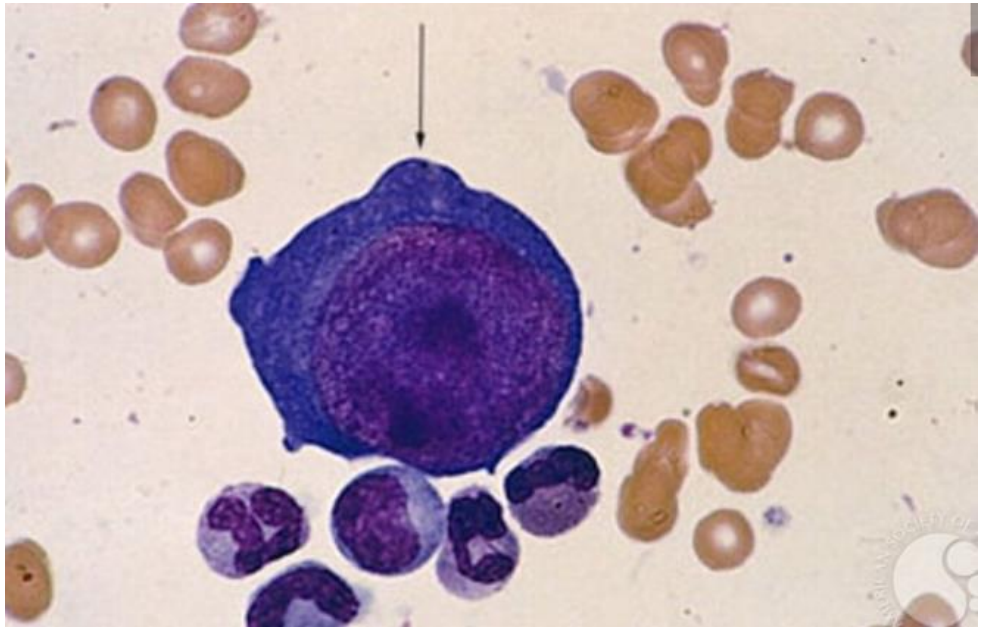
Immunocompetent individuals

- non-symptomatic
  - B19 mostly in tissues than in bone marrow
  - No viremia or anti-B19 IgM
  - Virus persist without replicating
- symptomatic
  - Myocarditis, cardiomyopathy
  - Chronic arthropathy
  - Liver failure

Corcioli F et al., J Med Virol. 2008; 80:2005-2011

Chronic red cell aplasia

- In immunocompromised patients
- Depletion of erythroid precursors in bone marrow
- Symptoms are generally not present



More common long-term persistency of B19 is in non-erythroid cells/tissues

Cardiomyopathy

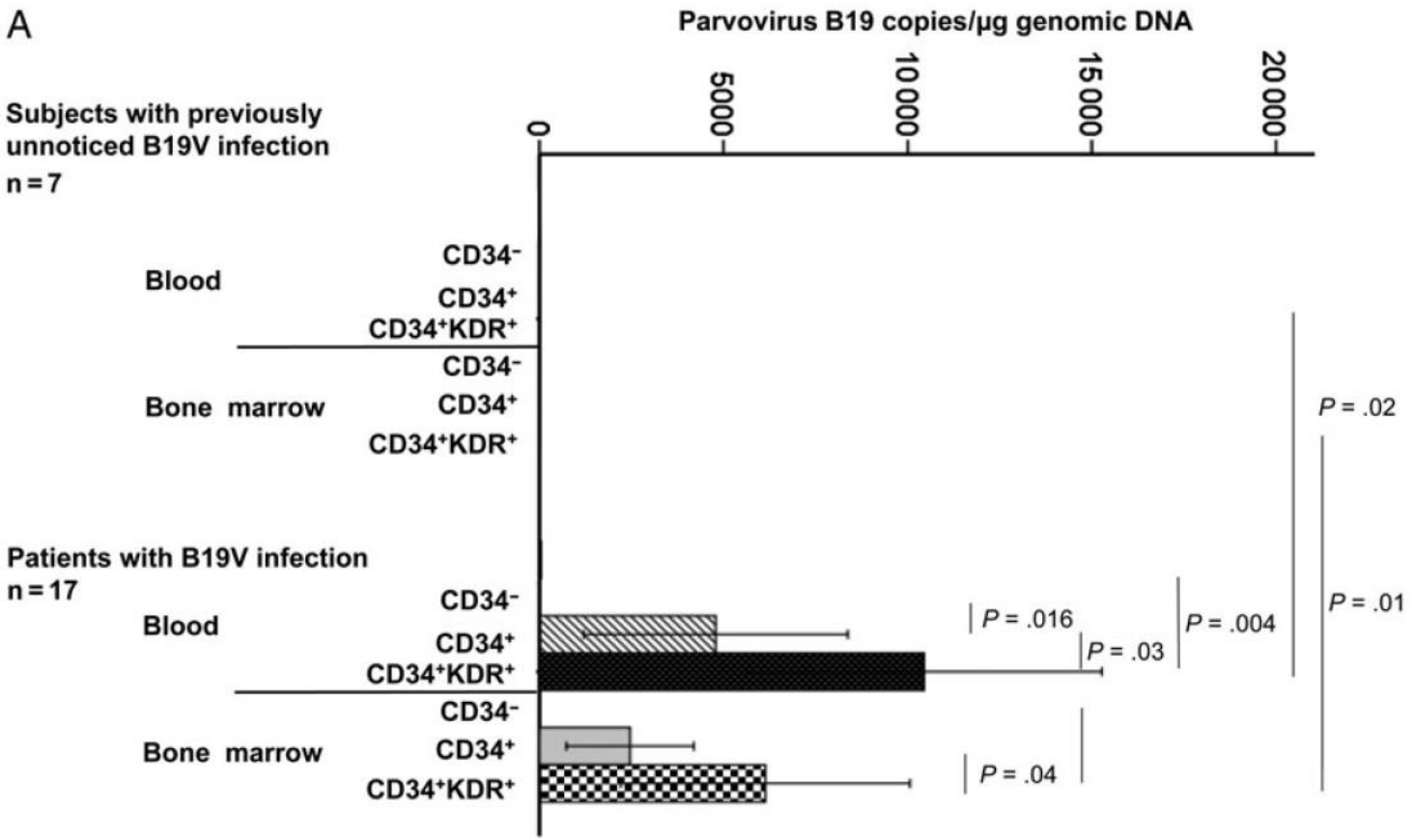
- B19 is a common pathogen in microvascular disease and cardiomyopathy
- Bone marrow-derived circulating angiogenic cells (CACs) = similarity with EPCs

CACs are characterized by surface antigen expression:

CD34 – hematopoietic marker

KDR (kinase insert domain receptor) – endothelial marker

Cardiomyopathy and CACs



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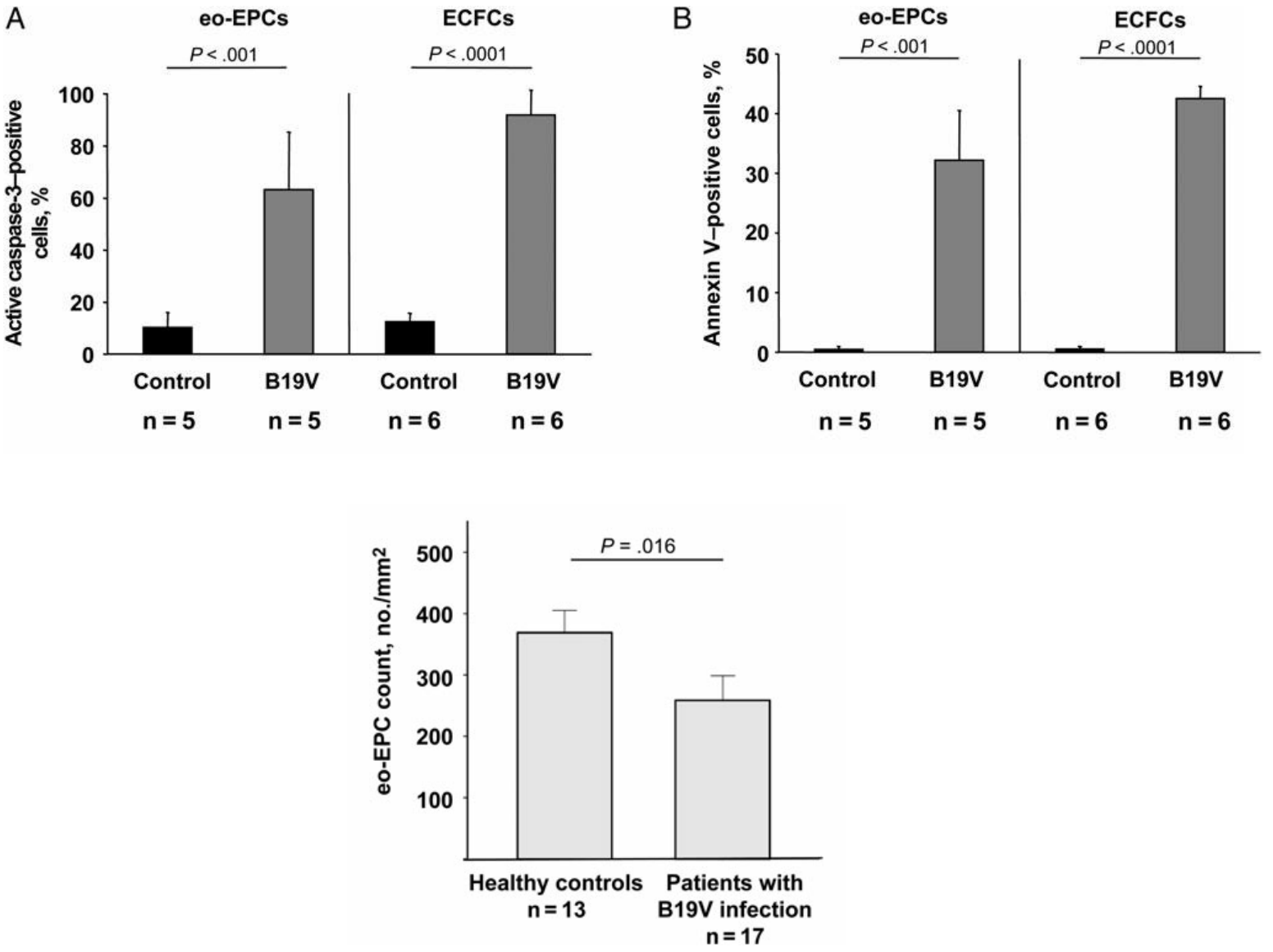
B19 induces apoptosis of CACs in cardiomyopathic patients



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Persistent B19 infection & diseases

- In 13 of 50 (26%) bone marrow samples from rheumatic patients indicating persistent infection

{Lundqvist A et al; 2005}

- Low-level viral gene expression occurs in some persistently infected cells
  - Bone marrow
  - Heart
  - Kidney
  - Liver – chronic hepatitis
  - Lymphoid
  - Thyroid tissues

{Mogensen TH et al; 2010}
{Adamson-Small LA et al; 2014}

presence of B19V DNA in blood not necessarily correlates with active B19 replication

Summary